REMARKS

This Amendment, filed in reply to the Office Action dated June 10, 2010, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1, 5, 8-9, 12 and 32-36 are all the claims pending in the application. Claims 2-4 and 6-7 are canceled. Claims 10-11 and 13-31 are withdrawn from consideration. Claims 1-9 and 12 are rejected. Claims 1, 5, 8-9 and 12 are amended herewith. Claims 32-36 are newly added. Exemplary support for the amendment to Claims 1, 5, 8-9, 12 and new Claims 32-36 can be found at for example page 19, line 26 to page 20, line 21; page 20, lines 18-21; page 29, lines 18 to page 30, line 3; page 32, lines 7-11; page 41, line 4 to page 42, line 8; page 51, line 14 to page 53, line 9; and Figure 6.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Foreign Priority

Applicants thank the Examiner for acknowledging Applicants' claim to foreign priority and indicating that all certified copies have been received.

Drawings

Applicants thank the Examiner for accepting the drawings filed on October 18, 2005.

Information Disclosure Statement

Applicants thank the Examiner for returning a signed and initialed copy of the PTO Form SB/08 that accompanied the Information Disclosure Statement filed October 18, 2005 and March 9, 2006, indicating consideration of the references therein.

RESPONSES TO REJECTIONS

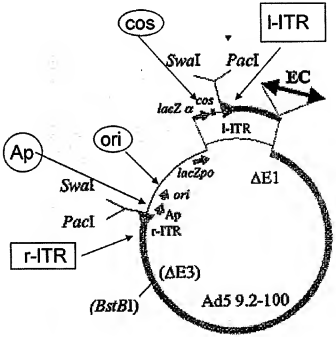
A. Claims 1, 5, 8-9, 12 and 32-36 are Patentable over Danthinne 2000

On page 2 of the Office Action, Claims 1-3, 5-8 and 12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Danthinne *et al.* (Gene Ther., 2000)("Danthinne 2000"). In particular, the Office Action states that Danthinne 2000 teaches the creation of a cosmid vector comprising an adenoviral genome with both right and left ITRs, an El deletion, and flanked by *Pac*I/*Swa*I restriction sites which are not found in the adenoviral genome. The Office Action further states that the cosmid comprises an ampicillin resistance gene, an origin of replication (*ori*), a spacer, and a cos region between the two ITRs. According to the Office, absent a limiting definition in the specification, the spacer sequence is arbitrarily chosen as a sequence between any of the above components, and accordingly, the ampicillin gene and *ori* are located between the left ITR and the spacer in Figure 1 of Danthinne 2000.

Applicant submit that Danthinne 2000 does not inherently or expressly disclose the presently claimed cosmid vector. Initially, Claim 1, as amended recites, a cosmid vector comprising *inter alia*, "a drug resistant gene, a replication origin, a spacer sequence and a COS region in this order from outside of the left-inverted terminal repeat sequence toward the right inverted terminal repeat sequence, (5) a second pair of identical restriction enzyme recognition sequences, one of which is present (i) within the E1 gene deletion side and (ii) at a right side of a foreign gene insertion site, wherein the right side is IVa2 gene side, and the other is present inside the spacer sequence, and wherein said cosmid vector being suitable for constructing, by being acted by a restriction enzyme recognizing the second pair of identical restriction enzyme recognition sequences, a plasmid in which a major part of the adenoviral genome, the spacer

region and the COS region are removed, while a foreign gene inserted at the foreign gene insertion site present in the E1 gene deletion site is maintained."

Danthinne 2000 does not describe the claimed cosmid vector. Danthinne 2000 teaches a cosmid vector containing a cos region, a replication origin (ori) and an ampicillin resistance gene from the outside of the left inverted terminal repeat toward the right inverted terminal repeat. See figure 1 on page 81 of Danthinne 2000, a portion of which is replicated below, with marking showing the location of cos, ori and drug resistance gene for the Examiner's convenience.



As illustrated above, the vector of Danthinne 2000 fails to teach the order of genes as presently recited. Indeed, Claim 1, as amended, incorporates the limitations of Claim 4, which was not rejected as being anticipated by Danthinne 2000. In particular, Claim 1, as amended recites, among other things, that "the drug resistant gene, the replication origin, the spacer

sequence and the COS region are arranged in this order from outside of the left-inverted terminal repeat sequence of the adenoviral genome toward a right inverted terminal repeat sequence." Support for the amendment may be found throughout the specification, at for example, page 20, lines 22-25, original claim 4 and Figure 6. Furthermore, Applicants attach hereto an illustration labeled "Annex 1" which illustrates the vector of the present invention. As illustrated in Annex 1, the vector comprises an adenoviral genome having a left-inverted terminal repeat and a right-inverted terminal repeat (labeled ITR); a deletion in an adenovirus E1 gene region (labeled $\triangle$E1); two pairs of identical restriction enzyme recognition sequences; a drug resistant gene (labeled Amp^r), a replication origin (labeled ori), a spacer sequence and a COS region in this order from outside of the left-inverted terminal repeat sequence toward the right inverted terminal repeat sequence.[2]

As Danthinne fails to teach the order of a drug resistant gene, ori, spacer sequence and the Cos region from outside of the left inverted terminal repeat sequence toward a right inverted terminal repeat sequence, Danthinne 2000 does not inherently or expressly disclose the presently claimed cosmid vector. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)).

Accordingly, Applicants respectfully request withdrawal of the rejection.

---

[2] Annex 1 (and Annex 2, described in detail below) is attached hereto to illustrate the difference between the prior art and an exemplary vector of the claimed invention and is not considered new matter or intended to further limit the present claims.

B. Claims 1, 5, 8-9, 12 and 32-36 are Patentable over Danthinne 2000 in view of Danthinne 1999

On page 3 of the Office Action, Claim 4[3] is rejected under 35 U.S.C. § 103(a) as being unpatentable over Danthinne 2000 as applied to Claims 1-3, 5-8 and 12 above, and in further view of Danthinne (J. Virol. Meth., 1999 ("Danthinne 1999")).

Although the Office Action acknowledges that Danthinne 2000 does not teach the precise arrangement of the components as recited in Claim 4, the Office relies on Danthinne 1999 for a teaching of a cosmid wherein the order of the ampicillin resistance gene, SV40 ori, spacer, and cos are arranged from the left ITR to the right ITR. The Office Action concludes that one of ordinary skilled artisan, seeking to prepare an adenoviral cosmid, would have been motivated to use the order of cosmid components as specified in Danthinne 1999 with the cosmids and methods of Danthinne et al 2000 because "both references teach these components to be well known and essential cosmid components, and the order of arrangement in relation to adenoviral LTRs to be a matter of design choice when preparing the cosmids from plasmid components." See page 4 of the Office Action.

Furthermore, Claim 9 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Danthinne 2000 as applied to claims 1-3, 5-8 and 12 above, and in further view of Miyake *et al.* (PNAS, 1996)("Miyake *et al.*").

Applicants respectfully disagree. Applicants note that in order to establish a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. § 2143. The factual inquiries which must precede a

[3] Although the Office Action states that Claim 5 is rejected under section 103, Applicants believe that this is a typographically error, and rather the rejection is directed toward Claim 4.

legal conclusion on obviousness are the determination of (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) objective evidence of nonobviousness, such as commercial success, long-felt but unsolved needs which the invention has satisfied, failure of others to make the claimed invention, copying of the alleged invention, and unexpected results brought about by the invention. See *Graham v. John Deere Co.*, 383 U.S. 1 (1966) and *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007).

Initially, as discussed above, Claim 1, as amended recites, *inter alia*, "a second pair of identical restriction enzyme recognition sequences, one of which is present (i) within the E1 gene deletion site and (ii) at a right side of foreign gene insertion site, wherein the right side is IVa2 gene side, and the other is present inside the spacer sequence, and wherein said cosmid vector being suitable for constructing, by being acted by a restriction enzyme recognizing the second pair of identical restriction enzyme recognition sequences, a plasmid in which a major part of the adenoviral genome, the spacer region and the COS region are removed while a foreign gene inserted at the foreign gene insertion site present in the E1 gene deletion site is maintained." As discussed throughout the specification, the recited arrangements and locations of the sequences in the claimed cosmid vector are important to maintain the foreign gene insertion site of the present invention, while a major part of the adenoviral genome, the spacer region and the cos region are removed. Support for the claimed amendments may be found throughout the specification, at for example, page 25, line 15 to page 26, line 4; page 41, line 4 to page 42, line 8; page 51, line 14 to page 53, line 9 and Figure 6. In particular, the instant specification, at page 41 states that "because of the presence of the drug resistant gene and the replication origin between the left terminal ITR of the adenoviral genome and the spacer sequence, it is possible to

easily construct a plasmid in which a major part of the adenoviral genome, the spacer region and the COS are removed (adeno removal) while the foreign gene insertion site is maintained to have the same nucleotide sequence as the cosmid vector into which a desired foreign gene has been previously inserted." Page 41, lines 13-25. Additionally, Figure 6 of present specification shows that that one of the restriction enzyme sequences (i.e., SalI) is present at the right side of a foreign gene insertion site and within the El gene deletion site, and that the other (i.e., SalI) is present inside the spacer sequence.

Neither Danthinne 2000 nor Danthinne (1999) teach or suggest the claimed vector.

First, as discussed above, Danthinne 2000 fails to teach or suggest the order of the cosmid vector claimed. To the contrary, Danthinne 2000 motivates one of ordinary skill in the art to a particular order, not the one that is presently claimed. On page 81, left column, Danthinne 2000 states that the "presence of the *cos* site next to the gene of interest rather than in the advenoviral plasmid guarantees the presence of the gene of interest in the resulting cosmid. The juxtaposition of the *lac*Z promoter/operator region next to the α-peptide coding region ensures the correct orientation of the insert relative to the adenoviral sequences." Thus, in view of the teaching of Danthinne 2000, one of ordinary skill in the art would not have been motivated to change the order of the cosmid vector. Danthinne 1999 fails to provide any motivation to one of ordinary skill in the art to change the order of the vector in Danthinne 2000. Additionally, it appears that the arrangement of the vector in Danthinne 1999 differs from the one presently claimed in that the left ITR is positioned next to the ori.

Second, it is well-settled that demonstration of an unobvious or unexpected property, or superiority of a property shared with the prior art, can rebut a case of *prima facie* obviousness. In particular, Applicants have demonstrated that the claimed cosmid vector, as described in the

specification and working examples provides unexpectedly superior results over other vectors in the prior art, in that the vector can be easily subject to the sequencing of a foreign gene to be inserted or the investigation on whether the foreign gene can be expressed.

The specification, at page 51, line 15 to page 53, line 9, at Example 3 describes the construction of a plasmid wherein the majority of the adenoviral genome and the expression of an inserted foreign gene is confirmed. Example 3 describes constructing cosmid vectors, pAxCARedEit and pAxCAGFPit, which are constructed with restriction enzyme SalI site and NruI site immediately upstream of the CAG promoter and within the spacer region. The plasmid, removing the majority of the adenoviral genome (containing about 0.4 kb from the left terminal), is constructed by self-ligation of these cosmid vectors after digestion with the restriction enzyme. To confirm whether the expression unit of red fluorescent protein (RedE) was accurately integrated in the cosmid vector pAxCARedEit, cells were transformed with the plasmid pxCARedEit. Two days after the transfection the red fluorescence was observed in numerous transfected cells by a fluorescent microscope (at excitation wavelength: 558 nm/radiation wavelength: 583 nm). As a result, it was confirmed that the RedE expression unit was accurately integrated in the cosmid vector pAxCARedEit.

Furthermore, the illustration in Annex 2, attached hereto, shows the characteristics of the cosmid vector and the advantageous effects of the claimed cosmid vector of the present invention. In particular, as shown on the upper left side of the illustration, the cosmid vector is digested by a restriction enzyme (for example, SwaI) recognizing the restriction enzyme recognition sequence contained in the E1 gene deletion site, thereby to insert the foreign gene and to generate the cosmid vector as shown on the upper right side of the illustration. Thereafter, as shown in the upper right side of the illustration, the cosmid vector is digested by a restriction

enzyme (for example, SalI) recognizing the two restriction enzyme recognition sequences, one of which is present at right side (IVa gene side) of a foreign gene insertion site and within the E1 gene deletion site, and the other is present inside the spacer sequence, to generate an adenoviral vector containing the foreign gene but removing a major part of the adenoviral genome, the spacer region and the cos region.

Finally, Miyake *et al.* fails to cure the deficiencies of Danthinne 2000 in view of Danthinne 1999. Miyake *et al.* is merely relied upon for a teaching the use of the CAG and EF-1α promoters in the cosmid vector. Miyake *et al.* fails to teach or suggest the claimed cosmid vector. Since the asserted combinations would not result in the claimed invention, as now recited, the claimed invention is not rendered obvious by Danthinne 2000 in view of Danthinne 1999 and Miyake *et al.*

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are respectfully submitted to be proper.

C. <u>The Claims are not substantial duplicates</u>

On page 6, the Office Action states that if Claim 5 is allowable, Claim 6 will be objected to under 37 C.F.R. §1.75 as being a substantial duplicate thereof. The Office Action alleges that Claim 6 merely recites an inherent property of the DNA sequence set forth in Claim 5, i.e. that it is recognized by the enzymes listed in Claim 6.

In the interest of compacting prosecution, Applicants herewith amend Claim 5 to recite that the cosmid vector comprises "the sequence TTCGAA, which can be recognized by at least Csp45I, BspT104I or BstBI, as a restriction enzyme recognition sequence present on both sides of the adenoviral genome." Claim 6 is herewith canceled. Accordingly, Applicants request withdrawal of the objection.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The U.S. Patent and Trademark Office is hereby directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

Azy S. Kokabi
Registration No. 58,902

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860
WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: October 12, 2010